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Prevention and treatment of venous thromboembolism in pregnancy in patients with hereditary antithrombin deficiency

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Objective: The aims of the study reported here were to provide data from six pregnant subjects who were enrolled in a clinical trial of antithrombin (AT) concentrate, discuss other published case series and case reports, and provide general guidance for the use of AT concentrate for inherited AT deficiency in pregnancy.

Methods: In the late 1980s, 31 AT-deficient subjects were enrolled in a prospective treatment trial of the plasma-derived AT concentrate Thrombate III®. Herein, newly available treatment data about the six pregnant subjects in the trial is tabulated and summarized.

Results: All six experienced venous thromboembolism (VTE) during pregnancy, were dosed according to a weight-based protocol, and were treated concomitantly with anticoagulation. Loading doses of AT concentrate of 54–62 units/kg were followed by maintenance doses of 50%–100% of the loading dose for 3–10 days. At the time of labor, loading doses of 46–50 units/kg were followed by maintenance doses of 50%–75% of the loading dose for 5–7 days. None of the six experienced recurrent thrombosis while receiving treatment with AT concentrate.

Conclusion: Currently we suggest that women with AT deficiency who are pregnant or postpartum and have a personal history of VTE or current VTE receive AT concentrates.

Keywords: thrombophilia, thrombosis, plasma-derived concentrate, labor, delivery, heparin.

Introduction

During pregnancy, women have a four- to five-fold increased risk of thromboembolism compared with women who are not pregnant.^{1,2} Eighty percent of thromboembolic events in pregnancy are venous,³ with an absolute risk of venous thromboembolism (VTE) during pregnancy of between 0.5 and 2.0 per 1000 women.^{3–9} The most important risk factor for VTE in pregnancy is a history of thrombosis. Besides this, the next most important risk factor for VTE in pregnancy is thrombophilia.^{3,10} Thrombophilia is present in 20%–50%^{11–13} of women who experience VTE during pregnancy and the postpartum period.

Antithrombin (AT) deficiency was the first inherited thrombophilia to be described in 1965.¹⁴ Since then, multiple reports have documented the association between inherited AT deficiency and an increased rate of VTE.¹⁵ In pregnancy, the rate is correspondingly higher. Historic case series have reported rates of 18%–70%.^{16–18} The variation in these rates can be attributed to the relatively small numbers in each series and to the varied definitions of AT deficiency. Although a systematic review including more recent studies (some with more liberal thresholds of AT deficiency and not all requiring a positive family history) found a lower risk of thrombosis in pregnancy than did the initial studies (odds ratio 4.76 [95% confidence interval 2.15, 10.57]); the high rates in

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the initial studies prompted obstetricians and hematologists to recommend full anticoagulation during pregnancy for women with AT deficiency.^{19,20} More recent recommendations from the American College of Chest Physicians do not endorse anticoagulation unless a woman has had a history of thrombosis, but continue to describe AT deficiency as a high-risk thrombophilia.²¹ Despite full anticoagulation during pregnancy and the postpartum period, women with AT deficiency are still vulnerable to developing VTE, particularly at the time of childbirth, when anticoagulation is withheld to prevent bleeding complications.

AT is a natural anticoagulant that inactivates thrombin by covalently binding to the active serine of thrombin and activated factor X (FXa).¹⁵ AT can also inactivate other coagulation factors, including factors IXa, XIa, and XIIa¹⁵ (Figure 1). AT has a binding site for heparin and, in the absence of heparin, has low inhibitory activity against thrombin. In contrast, when heparin is present, inhibitory activity can be induced at least 1000-fold.²² Importantly, in the absence of AT, heparin has little effect.

AT concentrates have been available since 1979.²³ Of the two AT concentrates currently available, one is purified from human plasma (Thrombate III®, Grifols Therapeutics, Clayton, NC, USA) and the other is a recombinant product produced in transgenic goat mammary glands (ATryn®, GTC Biotherapeutics, Framingham, MA, USA). Women with AT deficiency may be candidates for AT concentrates during pregnancy or the postpartum period when anticoagulation is desired, but contraindicated, for example during: invasive procedures such as egg retrieval, cerclage, chorionic villus sampling, or amniocentesis; miscarriages and ectopic

pregnancies; episodes of bleeding; surgical procedures; neuraxial anesthesia; childbirth, including cesarean delivery; postpartum tubal ligation; thrombocytopenia. AT concentrates can also be utilized to normalize antithrombin levels in women with current thrombosis or recurrent thrombosis despite anticoagulation.

AT deficiency is a rare disease affecting between 1 in 500²⁷ and 1 in 5000 individuals,²⁴ so large trials have not been conducted. The clinical trials that were conducted to obtain approval for AT concentrates were carried out on patients with inherited AT deficiency who were undergoing surgery or giving birth. In these small trials,^{26–28} efficacy was demonstrated by the low rate of thrombosis when anticoagulation was withheld during the perioperative or peripartum periods. Pregnant patients were included in these trials, but details that could provide guidance have not been published. The purpose of this paper is to provide detailed descriptions from six pregnant subjects in one of these trials, discuss the other published case series and case reports, and provide general guidance for the use of AT concentrates for inherited AT deficiency in pregnancy.

Methods

In the late 1980s, 31 AT-deficient subjects at high risk of thrombosis were enrolled in a prospective treatment trial of the plasma-derived AT concentrate Thrombate III®.²⁹ All participating sites had the approval of their respective institutional review boards. Of the 31 subjects, six were pregnant. Doses were based on the following formula:

$$\text{Dose (in units)} = (120\% \text{ minus basal \% of normal}) \times \text{multiplied by (weight in kg)/(1.4)}.$$

Plasma AT levels were generally measured 12 hours after the initial dose to ensure that the level remained above 80%.²⁹ If necessary, a second dose of AT was administered at that time. Once predictable peak and trough levels were achieved, daily maintenance doses of the AT concentrate were administered in the amount of 60% of the loading dose in order to maintain plasma AT levels in the range of 70%–120% of normal. Although these six cases were mentioned in the publication from the original study,²⁶ detailed descriptions were not published. Since that time, additional de-identified data have been made available by the sponsor. Detailed treatment data are provided in Table 1 and the cases are summarized in the “Results” section.

For the “Discussion,” a computer-assisted search of the SciVerse Scopus electronic database (which includes Embase, MEDLINE, and MEDLINE Daily Updates) from

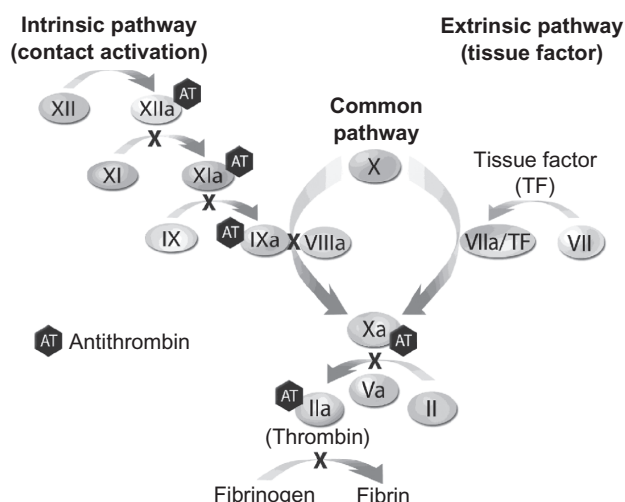


Figure 1 Antithrombin is inhibitory primarily to factors IIa (thrombin) and Xa as well as, to a lesser extent, to factors IXa, XIa, XIIa, and VIIa/TF.

1980 until February 2011 was conducted using different combinations of the following keywords: “antithrombin,” “ATIII,” “antithrombin deficiency,” “pregnancy,” “clinical study,” “prospective study,” “controlled study,” “complications,” “thrombophilia,” “thrombosis,” and “thrombotic complications.”

Results

Case 1

A 17-year-old woman with a strong family history of deep vein thrombosis (DVT) was admitted to the hospital at 20 weeks' gestation with right leg DVT and pulmonary embolism (PE). An emergency inferior vena caval ligation was performed and she subsequently received intravenous (IV) and, later, subcutaneous (sc) heparin for the duration of her pregnancy. She was admitted again at term for cesarean delivery. She was treated prophylactically with AT concentrate prior to delivery and for 6 days postpartum. The delivery and postpartum courses were uneventful, with no evidence of thrombosis.

Case 2

An 18-year-old woman was diagnosed with AT deficiency following DVT during her first trimester of pregnancy. Her plasma AT level was 38% at that time, and it was noted that both a brother and sister had histories of AT deficiency. She was maintained on sc heparin until admission for labor, when she was believed to be preeclamptic and in early labor. To raise her AT level, she received four units of fresh frozen plasma (FFP), but her plasma AT level remained at 48%. Therefore, the patient was given a loading dose of AT concentrate and was continued on heparin. The next day she was started on a maintenance dose of AT concentrate for 5 days. Her delivery (vaginal) and remaining hospital course were uneventful.

Case 3

A 23-year-old woman with a strong family history of AT deficiency had been treated with chronic oral anticoagulation since 11 years of age. She discontinued warfarin therapy because of pregnancy, but 1 month later, in her eighth week of pregnancy, was admitted to the hospital with massive thrombosis of the left leg. IV heparin treatment over 26 hours failed to raise the activated partial thromboplastin time (aPTT) above 51.5 seconds. Therefore, AT concentrate was administered with a loading dose. A daily maintenance course for 3 days was followed by a twice-weekly course with sc heparin over 19 days. Despite this regimen, her trough

plasma AT levels dropped to 50%–60%. Therefore, her AT concentrate dose was increased, resulting in trough plasma levels generally remaining above 70%. Subsequently, she was maintained on the new dose twice weekly with sc heparin every 8 hours for the entire duration of the pregnancy as well as postpartum, when she was bridged to oral anticoagulant therapy. The delivery (vaginal) was uneventful, without thrombotic complications.

Case 4

A 27-year-old woman, with known AT deficiency, was admitted to the hospital at 12 weeks' gestation with PE and right upper lobe pulmonary infarction. She had a strong family history of AT deficiency, with eight maternal aunts and uncles with documented AT deficiency, mostly with recurrent VTE. The patient was treated with two units of FFP and started on IV heparin after receiving a bolus. However, heparin treatment caused only transient increases in the aPTT, despite administration of another bolus within 12 hours. Therefore, AT concentrate was initiated with a loading dose, which increased the plasma AT level from 50% to 110%. The aPTT lengthened to 68 seconds, and subsequent measurements demonstrated much less variability than had been noted prior to initiating AT concentrate therapy. Within 3 days, the patient was symptomatically much improved. She continued to receive IV heparin and AT concentrate for 10 days. A maintenance program was begun that consisted of sc heparin and AT concentrate twice weekly. Ultimately, the aPTT, measured just prior to each AT dose, stabilized at >50 seconds and the AT concentrate was discontinued 41 days after initiation of therapy. After 1 month, AT concentrate therapy was resumed once weekly along with sc heparin. This regimen was continued until 4 weeks prior to delivery, after which the dosing frequency was increased to twice weekly. The delivery (vaginal) was uneventful, without thrombotic complications.

Case 5

A 28-year-old woman was first treated for bilateral DVT at 20 years of age. Approximately 6 years later, she became pregnant, at which time her warfarin treatment was stopped and sc heparin substituted, but she miscarried 1 week later. During follow-up, her plasma AT level was found to be as low as 18%. She became pregnant again 2 months later and was switched from warfarin to sc heparin every 8 hours. At approximately 9 weeks' gestation, she presented with a 2-day history of right thigh pain. She was diagnosed as having acute DVT, with laboratory parameters indicating

Table 1 Details of treatment of six antithrombin (AT)-deficient pregnant patients

Case	Age, years	Parity	Basis for diagnosis	Indication for treatment with AT during pregnancy	Plasma AT level prior to initial AT treatment (%)
1	17	0	Strong family history of DVT	DVT R leg and PE at 20 weeks' gestation	59
2	18	0	DVT early pregnancy (also with strong family history)	DVT early pregnancy	38 at time of diagnosis
3	23	0	Strong family history	Massive DVT L leg at 8 weeks' gestation	50
4	27	0	Strong family history	PE at 12 weeks' gestation	50
5	28	0	DVT age 20. Diagnosed after miscarriage on Coumadin	DVT R leg 8 weeks' gestation	18 at time of diagnosis
6	35	0	DVT and PE at age 23 and strong family history	PE 12 weeks' gestation	42

Abbreviations: DVT, deep vein thrombosis; FFP, fresh frozen plasma; IV, intravenous; IVC, inferior vena cava; L, left leg; PE, pulmonary embolism; PP, postpartum; R, right leg; sc, subcutaneous.

active disseminated intravascular coagulation. Following treatment with FFP, her plasma AT level was only 30%–46%. Her heparin therapy was discontinued, she was switched back to warfarin, and treatment with AT concentrate was started. A loading dose was followed with daily maintenance doses for the following 7 days. She then underwent termination of pregnancy without incident. Her DVT rapidly improved during treatment and she was discharged on warfarin anticoagulation.

Case 6

A 35-year-old woman with a history of DVT and PE at 23 years of age, as well as a family history of thrombosis (two sisters, a mother, and aunt had recurrent VTE), was admitted with PE at 12 weeks' gestation. Her plasma AT level was 58%. While being treated with heparin, she developed recurrent PE and was found to be heparin resistant. IV heparin was administered when her plasma AT level was 43% and

she was continued concomitantly on AT concentrate. She received a total of twelve daily infusions of AT concentrate. All infusions were well tolerated. Termination of pregnancy was performed 1 week after initiation of treatment. She was discharged 4 days later on warfarin therapy.

Summary

In this case series, the patients ranged in age from 17 to 35 years. None had given birth previously. Five of the six had a strong family history of AT deficiency and VTE. All of these patients developed and were treated for VTE during pregnancy. Except for one patient who was diagnosed in the current pregnancy and had an AT level of 18%, AT levels at the time of initial treatment ranged from 38% to 59%. Besides full anticoagulation with IV or sc heparin, four of the six patients were treated with plasma-derived AT concentrate at the time of diagnosis of VTE, two after receiving FFP. Loading doses of AT concentrate of 54–62 units/kg were administered. This was

Treatment in pregnancy	Weeks' gestation	Mode of delivery	Summary of procedures or AT concentrate for delivery
IVC ligation, IV and sc heparin	Term	Cesarean	Admitted at full-term for delivery. Given 50 units/kg loading dose. Repeated 72 h later. Heparin discontinued and cesarean performed. 25 units/kg daily \times 7 days thereafter. Heparin restarted 2 days PP. Coumadin started 4 days PP. Nadir AT levels prior to dosing were all approximately 80%. Discharged on Coumadin® (Bristol-Myers Squibb, New York, NY, USA)
sc heparin	Term	Vaginal	Admitted in early labor with preeclampsia. 4 units FFP on admission, AT level still only 48%. Given AT 46 units/kg loading dose. Maintenance of 34 units/kg \times 24 hours then 23 units/kg daily \times 5 days. AT levels 64%–122% Coumadin PP
IV heparin plus AT 54 units/kg loading dose, then 31 units/kg (60% of loading dose) \times 3 days, followed by 54 units/kg twice weekly plus sc heparin. Then sc heparin plus AT concentrate increased to 72–76 units/kg twice weekly to maintain nadir plasma AT levels $>$ 70%	Term	Vaginal	
2 units of FFP on admission. IV heparin plus AT 50 units/kg loading dose, then 33–50 units/kg \times 10 days. Then AT 40–66 units/kg twice weekly for 1 more month with sc heparin. Plasma nadir AT levels remained $>$ 66%. AT was discontinued for 1 month and resumed at 62 units/kg once weekly with sc heparin	Term	Vaginal	AT 62 units/kg increased to twice weekly in the 4 weeks prior to delivery. Coumadin PP
FFP on admission. AT level still only 30%–46%. AT 62 units/kg loading dose. Daily maintenance doses of 38–39 units/kg	9	Termination of pregnancy	Discharged on Coumadin
IV heparin plus AT 58.5 units/kg daily \times 3 days then 29.3 units/kg \times 8 days, then 58.5 units \times 1 day	13	Termination of pregnancy	Termination of pregnancy after 1 week of therapy. Discharged 4 days later on Coumadin

followed by a maintenance dose of 50%–100% of the loading dose for 3–10 days. Two of the four women who received AT concentrate terminated their pregnancies. The other two received an extended course with twice-weekly infusions – 62 units/kg in one case and 72–76 units/kg in the other – to maintain trough plasma AT levels $>$ 70%. One patient (who did not receive either FFP or AT concentrate) underwent inferior vena caval ligation. She and the other remaining woman only received AT concentrate at the time of labor, with a loading dose of 46–50 units/kg followed by a maintenance dose of 50%–75% of the loading dose for 5–7 days. None of the women experienced recurrent thrombosis while receiving treatment with AT concentrate (Table 1).

Discussion

In this case series of difficult-to-manage AT-deficient women with new-onset or recurrent thrombosis during pregnancy, plasma-derived AT concentrate was administered

to normalize AT levels during initial treatment of VTE or to provide thromboprophylaxis when anticoagulation was withheld at the time of childbirth. AT concentrate was well tolerated and none of the women experienced recurrent thrombosis while receiving treatment. Loading doses and maintenance doses were prescribed according to protocol, which succeeded in raising AT levels to \geq 60 IU/dL.

Other studies of pregnant patients with hereditary AT deficiency have been published. Two reported on pregnancy outcomes in cohorts of women with AT deficiency,^{32,33} one reported on the prevalence of AT deficiency among women with pregnancy-related VTE,³⁴ and a number of case series and case reports have reported specifically on the course and treatment during pregnancy of women with AT deficiency.^{27,28,32–45} (Table 2). Different regimens have been used for antepartum and peripartum thromboprophylaxis. Between 1981 and 1992, the published regimens for antepartum thromboprophylaxis or treatment were for sc heparin or oral

Table 2 Course and treatment during pregnancy of women with antithrombin (AT) deficiency

	Pregnancies, n	Hx VTE	Current VTE	Baseline AT levels	Antepartum prophylaxis	Recurrent VTE	Peripartum AT concentrate
Brandt ³²	2	1	–	50%, 65%	sc heparin	0	550 units
Hellgren et al ¹⁶	9	2	–	39%–52%	sc heparin	1	2000–5000 units (average dose 41 units per kg [range 37–46]) per infusion to maintain AT levels of $\geq 80\%$
Michiels et al ³⁴	2	0	–	42%, 55%	Oral anticoagulants	0	3000 units (1 of 2)
Samson et al ³⁵	1	1	0	20%	sc heparin	0	3000 units loading dose (50 units per kg); 1500 units (25 units per kg) 48 h later, then doses adjusted and repeated every 48 h to maintain AT levels $\geq 80\%$
De Stefano ³⁶	4	2	1	“Around 50%”	sc heparin + oral anticoagulants	0	2500–3500 units
Menache et al ²⁷	5	2	1	29%–65%	–	0	5–6 daily infusions of 30.4 to 93.0 IU/kg
Blondel-Hill and Mant ³⁷	2	2	0	46%, 62%	sc heparin	1	6 units FFP (1 of 2)
Kario et al ³⁸	1	1	0	–	3000 units AT concentrate 3 \times per week starting at 34 weeks' gestation	0	
Yamada et al ³⁹	2	2	0	50%, 59%	6000 units AT concentrate (1) and heparin + 1500 units AT concentrate (1)	1	
Grandone et al ⁴⁰	15	1/3 women	–	–	–	0	None
Tiede et al ²⁸	9	7	0	33%–58%			Loading dose 21–81 units per kg recombinant AT, maintenance infusions of 160–436 IU/kg/day \times 3–10 days
Hidaka et al ⁴¹	1	1	1	31%	sc heparin + 3000 units AT concentrate 2–3 \times per week target $\geq 70\%$	1	
Sabadell et al ⁴²	18	5/9 women	3 (untreated pregnancies)	33%–57%	12/18 with LMWH	0	“In labor”
Pamnani et al ⁴³	1	1	0	54%	LMWH	0	3091 units recombinant AT followed by 712 units per hour
Sharpe et al ⁴⁴	1	1	1	38%	LMWH + AT concentrate 2000–3000 units per day after sagittal vein thrombosis at 34 weeks		3000 units \times 3 days at delivery then 2000–3000 units per day \times 6 weeks
Kovac et al ⁴⁵	1	1	0	33%	LMWH	0	1 dose 50 units per kg

Abbreviations: Hx VTE, medical history of venous thromboembolism; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism; sc, subcutaneous.

anticoagulants.^{27,32–37} Subsequently, the only anticoagulant used alone for antepartum prophylaxis was low-molecular-weight heparin.^{42–45} There were two reports from Japan of AT concentrate being used for antepartum thromboprophylaxis. In two cases it was used alone,³⁸ and in one case it was used with heparin.³⁹ In one case, AT concentrate was used in conjunction with sc heparin for the treatment of VTE.⁴¹ In one

report, no AT concentrate was given at the time of delivery,⁴⁰ while, in another report, FFP was given but no AT concentrate.³⁷ In five reports, peripartum AT concentrate was given just at the time of delivery^{32,34,36,42,45} and in another five, AT concentrate was given for several days surrounding the time of delivery.^{16,27,28,35,43} One study reported the administration of AT concentrate for 6 weeks postpartum.⁴⁴ When doses

were repeated, they were repeated at varying intervals (eg, daily, every 48 hours, two times per week, three times per week). When AT concentrate was administered, in twelve reports, plasma-derived concentrate was used ($n = 47$ cases) and in two reports recombinant concentrate was used ($n = 10$ cases). For plasma-derived AT concentrate, reported doses ranged from 550 to 6000 units or were weight-based. In one report, loading doses of 50 units/kg were administered, with maintenance doses of 25 units/kg every 48 hours. For recombinant AT concentrate, loading doses ranged from 21 to 81 units/kg and maintenance infusions ranged from 160 to 436 IU/kg/day and were administered for 3–10 days²⁹ or, in one case report, 3091 units followed by a maintenance infusion of 712 units per hour.⁴³ As for indications, only 29/53 cases had a personal history of VTE, with the others diagnosed with AT deficiency based on a family history. Fewer (four) had current VTE.^{19,30,31,35,37–39–48}

Plasma-derived AT concentrates are well tolerated, with minimal adverse reactions, and pose an extremely low risk for transmission of infectious agents. (There have been no confirmed reports of infectious transmission with Thrombate III®). The initial dose is calculated as: initial dose = ([desired AT level – current AT level] × weight in kg)/1.4. Maintenance doses are then calculated using approximately 60% of the loading dose and are given once every 24 hours to maintain peak and trough AT activity levels in the range of 80% and 120%, respectively.¹⁵

With minor glycosylation differences, recombinant AT has an identical amino acid structure to endogenous AT. Differences in glycosylation, however, do not appear to elicit immune reactions. The clinical difference is in the mean half-life, which is estimated to be 10.49 ± 7.19 hours for recombinant AT, in comparison to 56.8–68.0 hours for plasma-derived AT.¹⁵ Therefore, recombinant AT is administered as a continuous infusion. In a study by Tiede et al, the initial dose was calculated as: $[(100 - \text{pre-treatment AT activity level in \%}) \times \text{body weight in kg}]/2.28$. Maintenance infusion (IU/h) is then calculated as: $[(100 - \text{pre-treatment AT activity level in \%}) \times \text{body weight in kg}]/10.22$.²⁸ The prescribing information for ATryn provided by GTC Biotherapeutics has the loading dose in pregnancy as: $[(100 - \text{baseline AT activity}) \times \text{body weight in kg}]/1.3$. The maintenance infusion (IU/hr) is: $[(100 - \text{baseline AT activity}) \times \text{body weight in kg}]/5.4$.⁴⁶

Conclusion

In contrast to the other reports in the literature, the six patients discussed here each had a personal history of VTE,

were dosed according to a weight-based protocol, and were treated concomitantly with anticoagulation. Limitations of this series are the relatively small number of cases and the fact that the cases were treated some time ago with anticoagulation regimens that have been replaced by low-molecular-weight heparin. Despite the fact that the series comprises only six cases, this is one of the larger series, and, as is true for other rare diseases for which randomized trials and even large cohort studies are unavailable, small case series or even individual cases can be instructive. Otherwise, there are few data and little guidance on the management of AT concentrates in pregnancy and at the time of delivery. General guidance regarding dosing has been provided here. Our current guidance would be that women with AT deficiency who are pregnant or postpartum and have a personal history of VTE or new-onset or recurrent VTE receive AT concentrates. We would suggest that women with low levels of AT ($<60\%$) with a compelling family history, and those with very low levels of AT ($<40\%$), also receive AT concentrates.

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Disclosure

The authors declare no conflicts of interest in this work.

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